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10/050,200	01/16/2002	Anne M. Fourie	ORT-1417	6279

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EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	**PAPER NUMBER**
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/050,200	FOURIE ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *04 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *04 July '03* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The Amendment of August 4, filed as paper 8 is acknowledged; the substitute specification and correction to figure 2 are acknowledged. The amendments to the claims and substitute specification have been entered. Claims 1-6 are cancelled. Claims 7, 9, 11-14, 17, and 18 are amended. New claims 20-21 are entered. Claims 7-21 are pending and are the subject of this Office Action.

DETAILED ACTION

1. Restriction/election

In response to the restriction requirement issued in the previous Office Action, Applicants confirmed the election of Group II claims 6-19 and cancelled claims 1-6 drawn to the nonelected invention.

2. Objections

2.1. Specification

Objections to the specification raised in the previous Office Action are withdrawn, because the substitute corrected specification has been filed. However, the Accession No. for aggrecanase –1 and –2 quoted on page 8, lines 12 and 13, are invalid. The correction of the accession number is required.

2.2. Claims

The objection to claims have been withdrawn, because the spelling of the term aggrecanase has been corrected.

2.2. Drawings

The objection to description to Fig. 2 on page 5 as illustration of "relative activities" of aggrecanase –1(A) and –2 (B) for 56 different FRET peptides is not withdrawn. It is unknown what Applicant mean by relative activities; relative to what? On page 16, line 5, Applicants write, "expressed in arbitrary, but relative units", which is still unclear.

Correction to Fig. 2 that missed the description of y-axis are accepted.

3. Rejections

3.1. 35 USC, section 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Rejection of claim 7-13 under 35 U.S.C. 112, second paragraph, made in the previous Office Action is withdrawn, because the claim has been amended.

The amended claims 7-13 are confusing for giving the terms "a truncated aggrecanase" and "aggrecanase" the same meaning. A truncated aggrecanase differs from its parental protein structurally, and may differ functionally as not every truncation is neutral for the enzymatic activity of the molecule. In the instant application (Fig.1) the

truncated forms of aggreccanase –1 and –2 (SEQ ID NOs: 8 and 9) consist of pro- and metalloprotease domains of both aggrecanase molecules. These truncated forms are unlikely to hydrolyze aggrecan because they do not contain the trombospondin motifs. The truncated aggrecanase-1 lacking the trombospondin motif 1 (TSP-1) is not effective in cleaving aggrecan; see Tortorella M. et al, J. Biol. Chem. 2000, august 18, 275/33, pages 25791-25797; enclosed to the Office Action and listed in the PTO Form 892.

The amended claim 9 is not finished. The claim will be examined as restricted to aggrecanase -1, because it is unclear what else was meant to be included as well.

Claim 13 is confusing, because a contacting step comprise already truncated aggrecanase, therefore, it is unclear how the contacting step can in addition comprise a cell expressing aggrecanase.

Claims14-16 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential step. See MPEP § 2172.01. The omitted step is a step comparing the activity obtained in the presence of the test compound to the activity obtained without the test compound.

The new claim 20 recites the phrase "a position of a complete native sequence" which is not defined by the claim or the specification rendering the claim indefinite.

2.2. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2.2.1. Lack of written description

Claim 7–21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 7-21 are rejected because neither the claims nor the specification teach that the inhibitor of the truncated form of aggrecanase inhibits also the full length enzyme. The full length enzyme is recited by preamble and the concluding step of the method, whereas the enzymatic reaction is performed by a truncated form of aggrecanase. Given the lack of evidence that disclosing an inhibitor of a truncated form is equivalent to disclosure of inhibitor of the full length enzyme Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Claims 7-9, 11-13 and 20-21 are directed to a method of use of a large and variable genus of peptides that are less that 40 amino acids in length wherein the

peptide comprises a cleavage site between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side polypeptides. Applicants disclose several representatives of the claimed genus identified by SEQ ID NOs: 3, 4, 5, 6 and 7. This is, however, insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Applicants fail to disclose any particular structure to function (of being cleavable by the truncated aggrecanase –1 and –2, i.e., SEQ ID NO: 8 and 9 or by any aggrecanase and its truncated form) relationship for a polypeptide that is less than 40 amino acids in length, wherein the peptide comprises a cleavage site between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side of said polypeptide. No information, beyond the characterization of SEQ ID NO: 3, 4, 5, 6 and 7 has been provided by Applicants, which would indicate that they had possession of the claimed genus of these polypeptides. The data presented in Fig. 2 clearly prove that predictability of the function of the representatives of the claimed genus is not apparent. The fact that a polypeptide of less than 40 amino acid long comprises a glutamic acid and as a neighbor on the C –terminal side of said glutamic acid a non-polar or uncharged amino acid is not sufficient for the polypeptide to be cleavable by SEQ ID NO: 8 or 9 or full length aggrecanase-1 and -2. In addition, it is even less apparent which of such polypeptides are the substrates for any aggrecanase, i.e. any truncated form, mutated form, and aggrecanases from different animal species.

Given the lack of structural characteristics of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Claims 7-8, 10-17 and 19-20 are directed to a genus of methods of using any truncated aggrecanase or any aggrecanase. Applicants disclose two representatives of truncated forms of aggrecanase-1 and -2 set forth by amino acid sequence of SEQ ID NO: 8 and 9, which are metalloprotease parts of human aggrecanase-1 and 2 (ADAMTS-4 and ADAMTS-5). However, the claims are not limited to the truncated forms of aggrecanases consisting of metaloprotease domains. Thus, the description is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed large and variable genus of methods encompassing use of any aggrecanase or its truncated form from any natural and man-made source. Not every truncated form of aggrecanase retains its activity, which, by definition is degrading of aggrecan. For example, a truncated form of aggrecanase-1 lacking the trombospondin motif 1 (TSP-1) is not effective in cleaving aggrecan; see Tortorella M. et al., J. Biol. Chem. 2000, August 18, 275/33, pages 25791-25797; enclosed to the Office Action and listed in the PTO Form 892.

Applicants fail to disclose any particular structure to function relationship identifying the genus of truncated polypeptides to be used in the claimed methods. Given the lack of structural characteristics of additional representative species of

truncated aggrecanases as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Newly added claim 21 is directed to a genus of method using homologues of SEQ ID NO: 8 and 9. The specification and original claims fail to quote any homologs of SEQ ID NO: 8 and 9. Thus the limitation "homologues" in claim 21 consists a new matter.

In their response to rejection under 35 USC first paragraph Applicants submit,

> "the specification provides adequate written description for the claimed invention. The specification discloses (1) that **out of 56 peptides**, the inventors identified **two peptide** sequences that were particularly preferred for their ability to be cleaved by aggrecanse-2, (2) that **one of the two peptide sequences**, which was particularly preferred for its ability to be cleaved by both aggrecanase-1 and –2, was used to optimize and assay and (3) that the assay was used for the identification of small molecule inhibitors of aggrecanase-1 and –2. See page 5, lines 26-33. The identified peptides have specific functional properties, namely, (1) they are less than 40 amino acids in length,(2) they comprise a cleavage site between a

> glutamic acid on the an [sic!] N-terminal side of the cleavage site, and a non-polar or uncharged amino acid residue on the a [sic!] C-terminal side of the cleavage site and (3) they are cleavable by a truncated aggrecanase [emphasis added]."

Applicants' arguments have been fully considered, but are found not persuasive. The rejected claims are generic for the peptides to be used as substrates, and in their arguments Applicants themselves state that **out of 56 peptides**, the inventors identified **two peptide** sequences that were particularly preferred for their ability to be cleaved by aggrecanse-2, (2) that **one of the two peptide sequences**, which was particularly preferred for its ability to be cleaved by both aggrecanase-1 and –2. Thus 1 out of 56 candidate peptides, i.e. less than 2% species of the genus occurred to be the proper substrate. As stated in the previous Office Action, paper No. 7, and reiterated above, the lack of structural characteristics of additional representative species as encompassed by the claims, is a proof that Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

2.2.2. Scope of invention

Claim 7-21 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for methods to detect compounds that inhibit aggrecanase using peptides of SEQ ID NO: 3, 4, 5, 6 and 7, that are cleavable by

polypeptides of SEQ ID NO: 8 and/or 9 and human aggrecanase –1 and -2, does not reasonably provide enablement for methods to detect compounds that inhibit any aggrecanase using any peptide less that 40 amino acids in length comprising a cleavage site for any aggrecanase, its truncate forms and their homologs, wherein said site is located between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side polypeptides.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompass any method of identifying an inhibitor any anaggrecanase using any peptide less than 40 amino acids in length and comprising a cleavage site for any form of truncated or full length aggrecanase form any natural or man-made source, wherein said cleavage site is between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side polypeptides.

Providing any truncated or full length aggrecanase covered by the scope of the invention requires cloning extremely large number of genes originating from any animal or gene bank. The genes should be subsequently expressed in their full length or any truncated form and the encoded polypeptides tested for aggrecanase acitivity using a standard substrate, i.e., the aggrecan fragment of more than 40 amino acids comprising as the cleavage site Glu-Ala mimicking residues Glu373-Ala374 of aggrecan molecule. After being successful in these lengthy and tedious procedures that are out of realm of the routine experimentation in the art, one skilled in the art has to design the polypeptides with the desired characteristics and test them for being a substrate for any of aggrecanases of their truncated forms.

While providing a peptide with claimed characteristics as a candidate substrate for an aggrecanase, has certain probability of success, Applicants' own investigations indicate that this probability is low. Applicants' data presented in Figure 2 provide an evidence that in case of aggrecanase-1 the probability is about 10% (6/56, taking those polypeptides for which the activity of cleaving is about 0.1 units) and in the case of aggrecanase-2 is even less, about 7% (4/56, taking into account those peptides for which the activity of cleaving is about 0.5 units). The probability of finding a peptide with the described characteristics that is a substrate for any aggrecanase is even less, because Applicants' own data from Fig. 2 indicate that the probability of finding peptide that is a substrate for both aggrecanases is about 3/56, i.e., about 6%; see also page 5, line 31 of the specification where Applicants state, "One peptide [out of 56 tested, MW]

was a good substrate for both truncated aggrecanase –1 and truncated aggrecanase – 2." The one peptide out of 56 is less than 2%.

Examiner concludes that without the further guidance on the part of Applicants regarding the structure of aggrecanases, their truncated forms and their substrates used in the claimed methods experimentation left to those in the art are improperly extensive and undue.

In their Remarks/ Arguments Applicants do not directly address the scope of enablement rejection made in the previous Office Action and maintained herein. To the extend their remarks, as quoted above, can be applied to the rejection for scope of enablement, Applicants attentions is turn to the fact that because the probability of finding the peptide having the described properties and being the substrate for any aggrecanase from any source or man-made, as well as its any truncated form and any homolog of the truncated form, is low, the undue experimentation is necessary unless the additional guidance regarding the structure of substrate and aggrecanase /its truncated form are provided. Thus, the rejection is maintained.

2.3. Rejection under 35 USC section 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 7-9,11-13 and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tortorella et al. (The trombospondin motif of aggrecanase-1 (ADAMTS-4) is critical for aggrecan substrate recognition and cleavage, J. Biol. Chem. 2000, August 18, 275/33, pages 25791-25797) in view of the common knowledge in biotechnology.

The claims are directed to

"A method to identify a compound that inhibits aggrecanase activity using a peptide less than 40 amino acids in length wherein the peptide comprises a cleavage site between a glutamic acid on an N-terminal side of the cleavage site and a non-polar or uncharged amino acid residue on a C-terminal side of the cleavage site and wherein the peptide is cleavable by a truncated aggrecanase; and detecting cleavage of the peptide wherein inhibition of peptide cleavage in the presence of a test compound indicates compound inhibtion of aggrecanase enzymatic activity."

Tortorella et al. disclose (page 4, line 3, of the Internet print out of the article) polypeptide NITEGE-ARGS consisting of less than 40 amino acids and comprising cleavage site E-A i.e. cleavage site between a glutamic acid on an N-terminal side of the cleavage site and a non-polar or uncharged amino acid residue (in this case alanine) on a C-terminal side of the cleavage site. Tortorella teach that both, the full-

length and truncated aggrecanse-1 cleave that substrate. Tortorella et al. does not tech the use of this peptide for identification of inhibitors of aggrecanase/its truncated form.

It would have been obvious for those skilled in the art to have the peptide disclosed by Tortorella et al. as a substrate for truncated aggrecanase and use it for screaning for inhibitors of the aggrecanase. The motivation would have been to have in the method a substrate easily available in large quantities and easy to handle in opposite to the native substrate, which is aggrecan isolated from human cartilage. The expectation of success is very high because Tortorella et al. have demonstrated that the peptide is the proper substrate for truncated and full length aggrecanase.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

3. Conclusion

All claims are rejected. No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Patent Examiner

Art Unit 1652

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